

A Multidisciplinary Approach to the Management of Hormone-Refractory Prostate Cancer

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The patient with hormone-refractory prostate cancer (HRPC) presents unique management challenges for both the urologist and the medical oncologist. Because of a lack of effective treatment options, the management of patients with HRPC has historically been palliative. Over the past 10 years, the advent of relatively efficacious chemotherapeutic regimens, particularly taxane-based chemotherapy, has resulted in a desire to treat patients with HRPC more aggressively. The complex needs of these patients have made a multidisciplinary approach, inclusive of specialists with expertise in disease processes directly affecting the patient, the optimal means of treating HRPC. An understanding of the natural history and complications of HRPC, combined with a systemic evaluative process, can allow the multidisciplinary team to comprehensively address the needs of the individual patient with HRPC.

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Conventional therapy for newly diagnosed metastatic prostate cancer has not changed greatly over recent decades. Since it was initially clinically described, hormonal ablative therapy has remained the mainstay of treatment for individuals with known metastatic disease or evidence of systemic recurrence after local therapy. When used, surgical or pharmacologic castration results in a decrease of serum prostate-specific antigen (PSA) and disease stabilization

Table 1
The Most Frequent
Symptoms Impacting
on Quality of Life in
Patients with Hormone-
Refractory Prostate Cancer

- Pain
 - Bone pain
 - Visceral pain
 - Local (prostatic) pain
- Fatigue
- Depression
- Urinary obstruction/retention
- Hematuria
- Hydronephrosis/azotemia
- Spinal-cord/nerve-root compression

in 85%–90% of patients. Symptoms such as bone pain and neurologic compromise are initially relieved in the majority of such patients. Local symptoms, including urinary retention, can be relieved in approximately 50% of patients with advanced prostate cancer through hormonal ablation alone.^{1,2}

The median response to hormonal ablative therapy in patients with known metastatic disease has been reported to vary between 18 months and 3 years.³ At the point of progression, defined by a rising serum PSA, the disease is generally termed hormone-refractory prostate cancer (HRPC) or androgen-independent prostate cancer, although an opportunity for response to second-line hormonal interventions may exist. The likelihood of symptomatology at the time of progression varies depending on the extent of the disease before hormonal therapy. Longevity following progression has historically been short, with a reported median of 6–9 months, given the lack of efficacious treatment options.

Traditionally, management of individuals with HRPC has been palliative, with careful attention paid to the control of pain and some preservation of quality of life. Whereas the medical oncologist generally carries the responsibility of managing palliative care, the urologist maintains some role in managing local symptoms and urinary function. Given the emergence of potentially efficacious treatment options, particularly taxane-based chemotherapies^{4–11}, a more coordinated strategy of treatment that focuses on systemic therapy for disease control, in combination with aggressive local therapy for the relief of symptoms, is desirable.

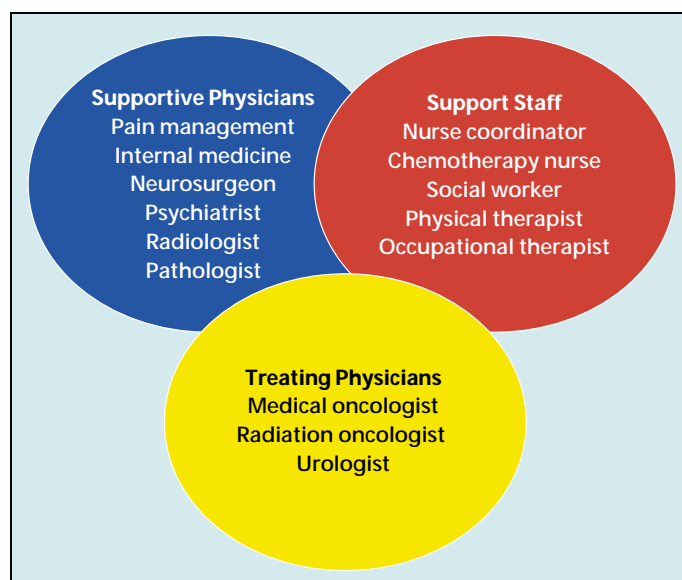
The patterns of disease progression in patients with HRPC can vary greatly from patient to patient, but knowledge of the likely sequelae of disease can be of great help in counseling patients at the time of relapse (see Table 1 for a list of the most frequent symptoms that affect a patient's quality of life). As bone represents the most common site of disease progression, bone pain remains the major insult to the quality of life in the prostate-cancer patient. Some

50%–75% of patients with HRPC experience bone pain, and a number may never have pain adequately controlled.^{12,13} A careful assessment of pain on a weekly basis and the use of nonsteroidal and narcotic pain medications, selected focal radiation, and aggressive systemic therapy may all be helpful in controlling pain and minimizing the impact of pain on quality of life.

Neurologic compromise secondary to spinal-cord compression is an important complication of HRPC that must be recognized at an early stage.¹⁴ A routine neurologic exam and careful radiologic monitoring of known spinal metastases can aid in this goal.

Local urinary symptoms can affect a large number of patients with androgen-independent disease. For those with the prostate in place, urinary retention, recurrent hematuria, dysuria, incontinence, and ureteral obstruction can be quite debilitating. With its potential for prolonged longevity relative to historical controls, aggressive local therapy to improve voiding function and protect against renal compromise has

Figure 1. A multidisciplinary approach to the management of patients with hormone-refractory prostate cancer.



become more relevant in the treatment of patients with androgen-independent disease.

Other common systemic sequelae of HRPC include fatigue, anemia, anorexia, and, on rare occasions, bleeding secondary to a disseminated intravascular coagulation (DIC)-like syndrome.¹⁵ The advancement of a locoregional tumor can result in secondary rectal obstruction, lymphedema, or deep venous thrombosis. Each has the ability to impact on the patient's performance status and ultimate ability to tolerate cytotoxic therapy.

The Role of Multidisciplinary Interaction

Given the emergence of potentially efficacious treatments for HRPC, there is a need for multidisciplinary management of patients. Interaction between not only treating physicians, but between supportive and ancillary services as well, lays the groundwork for a comprehensive treatment strategy that addresses the individualized needs of the patient (see Figure 1).

The basic tenet of multidisciplinary management is the recognition of the complex needs of the patient with androgen-independent disease. Patients may have differing goals for therapy, ranging from a desire to pro-

clinic with physicians of differing specialties and expertise. In this way, patient issues can be addressed as they occur. Information regarding recent tests, responses to therapeutics, and adverse events can be available from a single chart and shared among practitioners without delay. From a

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practical standpoint, the patient, often debilitated by cancer-related symptoms, can limit trips to the hospital and doctors' offices through the integration of services at a single site.

In many centers, a common clinic may not be an option because there are limited resources and conflicting schedules. In such cases, communication between managing physicians is critical in order to maintain continuity in the care of the individual patient. Ancillary services such as pain management, psychological counseling, social work, and nutritional counseling may be best situated at a doctor's clinic where they will be most needed. A weekly conference of all involved services can be an excellent conduit for the exchange of

to come. Alterations in the approach to treating the patient can be made preemptively.

Another important role of the multidisciplinary program is the creation and execution of experimental approaches to the disease. The implementation of clinical trials within a

multidisciplinary approach to androgen-insensitive disease is advantageous from several standpoints. Accrual to trials is improved by the team approach to recruitment. A large number of patient referrals often exist in such clinics. Whenever aggressive chemotherapy strategies are utilized, individuals who fail treatment or ultimately stop responding may benefit from the availability of experimental approaches. The underlying goal of the multidisciplinary team approach is the advancement or improvement of existing treatment strategies, and the implementation of clinical trials facilitates this goal.

The Role of the Medical Oncologist

Currently, the medical oncologist represents the central member of the multidisciplinary team because most treatment strategies will revolve around the delivery of some systemic therapy. Several chemotherapeutic treatment strategies have been developed based upon preclinical observations.^{4,5,7-11,16,17} Because many of these regimens demonstrate > 50% response rates in phase I and II evaluations, the choice of therapy will clearly be based on the patient's condition, performance status, and pre-existing comorbid conditions, as well as on the pre-existing bias of the treating physicians.

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long survival to simple palliation of pain and urinary compromise, and these goals must be sought out from the time of the initial management of the patient.

Multidisciplinary interaction can be constructed in a number of ways depending on the institutional set-up and resources. In the optimal setting, patients can be seen in a common

information and coordination of care. In such cases, a nurse coordinator generally acquires information regarding new and established patients, and a progress report is given. A discussion of disease-related progression and the patient's condition and response to therapy can then allow the patient to be directed to the appropriate services in the week

Because the medical oncologist takes a primary role in the treatment of men with HRPC, it is important for the oncologist to develop a specialized understanding of prostate cancer, inclusive of the management options for early-stage disease. Medical oncol-

counsel regarding treatment options. Despite having a relative lack of familiarity with chemotherapy and other forms of advanced therapeutics, the urologist may be called upon to guide the patient in exploring treatment options. Communication

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ogists who are in training should be exposed, like urologists and radiation oncologists, to patients who are deciding on and going through treatments for localized prostate cancer. Individuals with treatment-related side effects often have different perspectives on disease from those presenting with metastatic disease. Similarly, management issues may differ among individuals with the prostate in place or removed, treated with surgery or radiation, or faced with early recurrence as opposed to delayed. For this reason, it is extremely helpful for medical oncologists, particularly those specializing in prostate cancer, to remain well-versed in such issues.

After evaluating the patient and enlisting him in a particular treatment regimen, the medical oncologist is often the physician who has the most frequent interaction with the patient. It is therefore important that he or she be able to recognize and identify urologic and other disease-related problems as they occur.

The Role of the Urologist

The urologist has a unique role in the management of patients with HRPC in that the urologist often has had the longest history with the patients, having treated them through the earlier stages of disease. Such a pre-existing relationship may be of great importance to the patient seeking

with the other members of the multidisciplinary treatment team will allow the urologist to supply valuable and consistent advice.

A critical role for the urologist is in the management of local urinary symptoms. Patients with HRPC often present with local symptoms such as urinary obstruction or retention, hematuria, dysuria or pelvic pain, or ureteral obstruction. The aggressiveness of treatment in such cases must be balanced against the overall prognosis of the patient and the urgency of need for other treatment modalities such as focal radiotherapy or systemic chemotherapy.^{18,19} Although medical therapies can aid in cases of urinary retention, channel transurethral resection or suprapubic tube placement is often necessary. Surgical interventions should not delay necessary systemic therapies, as these will likely impact on longevity the most; but maintenance of urinary tract function may be essential in allowing the patient to tolerate aggressive therapy and judicious use is important.

The management of ureteral obstruction caused by locally advanced prostate cancer can be a challenging dilemma. Several reports have emerged on the utilization of metal stents or sheaths, but technical difficulties occur in the placement of the stents.²⁰⁻²² In our center at New York University Medical Center, if a

patient cannot easily pass a retrograde stent, we have taken the approach of performing percutaneous nephrostomy to regain renal function. This is followed by an attempt at stent internalization in an antegrade fashion a few weeks later. An internal/external stent provides a "safety valve" for decompression of the upper tract should sepsis or renal insufficiency occur. In patients with a bilateral obstruction, decompression of the upper tracts is necessary,²³ both to maintain survival and to preserve renal function for the delivery of cytotoxic chemotherapy, particularly if such therapy is platinum-based. In patients with a unilateral obstruction, careful discussion with the oncologist and the patient will help in making a treatment decision.

Pre-existing treatment-related side effects may also impact on the quality of life of patients with HRPC. Incontinence or voiding dysfunction from previous surgery or pelvic irradiation, erectile dysfunction, or urethral strictures will continue to be bothersome in the setting of systemic therapy. The tendency to overlook such problems as the disease-stage progresses should be avoided.

The Role of the Radiation Oncologist

The radiation oncologist plays an important role in the management of pain in patients with HRPC and bone metastases. It has been estimated that more than two thirds of patients with HRPC will have pain related to bone metastases at some point in their disease progression. Palliative focal radiotherapy can be quite effective in the management of such patients, particularly in those with limited bone disease and focal pain attributed to a single metastasis or a cluster of metastases.^{24,25} Low-dose (8–35 Gy) radiation is quite well tolerated, even in the setting of ongoing

ing or planned chemotherapy. Pain relief is generally achieved, and the effects can last upwards of 6 months.

In patients with existing or impending neurologic compromise caused by spinal metastases, the radiation oncologist plays a critical role in treatment. Decisions regarding radiotherapy versus neurosurgery are made based on the location of the lesion in question, the degree of epidural compression, and the stability of the surrounding bone.¹⁴ An impending fracture may also be a consideration in large bone lesions of the femoral neck or other weight-bearing locations, but in the setting of blastic bone lesions, this is not a common reason for focal radiotherapy.

A good example of the importance of multidisciplinary interaction is in the use of strontium-89 (Metastron®, Amersham Health Inc., Princeton, NJ), an injectable radioisotope that localizes to areas of bone turnover.^{26,27} Reported to be effective in reducing bone pain in more than one-half of patients, this agent's shortcoming is a transient, often incomplete, control of pain and the potential for myelosuppression. In patients who are scheduled to receive, or are already receiving, systemic chemotherapy, strontium-89 should be avoided in order to prevent excessive myelosuppression. With this in mind, careful treatment planning among specialties will provide for the selection of the optimal treatment.

The Role of Other Medical Specialties

The overall medical condition of the patient with HRPC is critical in determining the utility of individual therapies. Systemic agents carry potential side effects; therefore, the condition of the patient needs to be assessed and optimized before therapy is given. In patients receiving taxane-based therapy, some consideration of base-

line cardiac and neurologic function can be helpful in the selection of appropriate candidates. Similarly, optimization of pulmonary, renal, and neurologic function can be helpful in assessing not only which patients might tolerate therapy, but also which therapies might be appropriate options in individual patients. In a recent evaluation of patients with advanced cancer, 81% were found to have comorbid disease; of

that help the patient to manage such issues may be of equivalent importance to medical interventions in relieving patient stress.

The evaluation and treatment of pain is an essential component of the multidisciplinary approach to HRPC. More than two thirds of patients will likely experience pain at some point in their disease progression. Nonsteroidal and narcotic pain medications are the mainstay of pain control. Careful

Decisions regarding management of finances, care of dependents, and stresses on family members are among the greatest concerns affecting advanced cancer patients.

these, 59% had cardiac disease and 17% had pulmonary disease.²⁸ Considering this, routine evaluation of patients by a general internist or specialist well-versed in the specific morbidity of selected therapies is extremely helpful in the multidisciplinary setting.

The Role of Supportive and Ancillary Services

An assessment of the psychosocial needs of a patient before therapy is essential in selecting the appropriate therapy, in determining the ability of the patient to comply with therapy, and in planning for the inevitable progression of disease. An evaluation of supports, help at home, and the ability of the patient to travel to and from the treatment center will identify obstacles to care before the onset of therapy.

Patients often have concerns about their ability to continue with work or business-related responsibilities. The decisions regarding management of finances, care of dependents, and stresses on family members are among the greatest concerns affecting advanced cancer patients. Providing avenues of support and counsel

monitoring of pain and the escalation of pain medications may be most effectively carried out through the inclusion of a pain management specialist in the treatment team.

As a result of the multitude of physical and psychological stressors affecting the patient with HRPC, many patients with advanced cancer suffer from depression. The relief of stressors through discussion and implementation of support plans may be enough to reduce clinical depression. Effective strategies for pain relief and aid with physical impairment may complement such treatments. In many cases, the use of pharmacologic therapy may be necessary, and the inclusion of a psychologist or psychiatrist in the treatment team is essential.

Multimodal Treatment Strategies

In the approach to the patient with HRPC, the likelihood and nature of the disease progression, the available treatment options, and the realistic expectations of the outcome of treatment should be carefully discussed. It is easier to make a decision about treatment in symptomatic patients. In patients who are largely asymptomatic

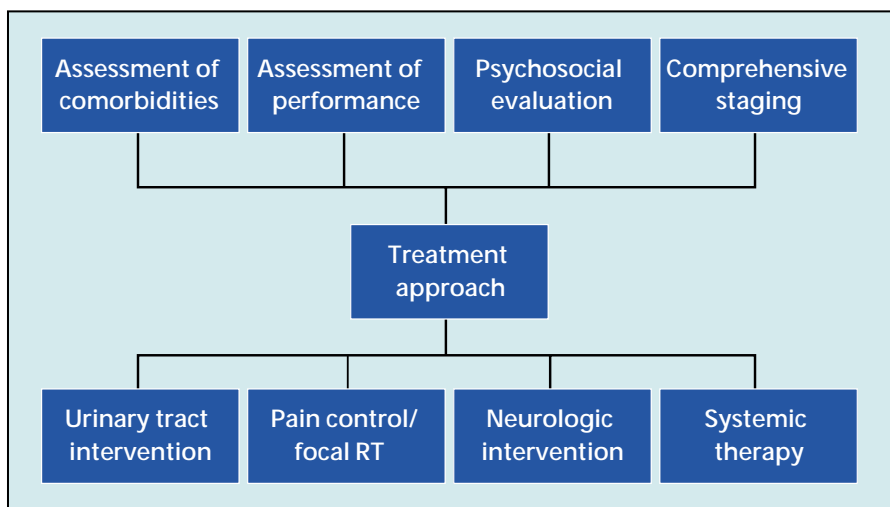


Figure 2. A multimodal approach to evaluating and treating a patient with androgen-insensitive prostate cancer. RT, radiation therapy.

matic, however, there is a desire to balance disease control with preservation of quality of life. For this reason, at NYU we have been reluctant to institute cytolytic chemotherapy "prophylactically" in individuals who do not have evaluable disease. Ultimately, a plan dictating the level of aggressive therapy or intervention should be developed for the individual patient, based on the treatment philosophy of the physicians and the desires of the patient himself.

Once a general approach has been constructed, the feasibility of specific treatment options must be assessed (see Figure 2). The first evaluation should be medical, with a careful delineation of comorbidities and performance status. An intervention to maximize the patient's medical condition must be balanced against the patient's life expectancy and his likelihood of tolerating aggressive therapy based upon performance status.

Next, the patient should undergo a psychosocial evaluation with a determination of available supports, living situation, transportation needs, and financial concerns. In doing so, careful attention should be paid to determine the likelihood of the

patient's compliance with potentially toxic therapies and need for long-term care or visiting nurses, as well as the patient's attitudes toward pursuing an aggressive therapy regimen. Such an evaluation is particularly important in selecting patients for clinical trials in order to avoid early drop-outs or failures to comply with the necessary follow-up.

Spinal pain presents a scenario of particular concern because of the possibility of spinal-cord compression.

A careful assessment of pain should also be carried out. For this purpose, a number of validated pain-scoring instruments exist. The value of using an objectified scale is several-fold, but most importantly, it will allow for an accurate means of following the progression and response to therapy. The control of pain at baseline is ideal, as it improves performance status and allows for the maximal likelihood of tolerating therapy. Spinal pain presents a scenario of particular concern because of the possibility of spinal-cord compression. If neurologic compromise

resulting from nerve-root compression is noted, this also must be dealt with before systemic chemotherapy is instituted.

The side effects of ongoing therapies should also be evaluated. The benefit of continued hormonal ablative therapy (using luteinizing hormone-releasing hormone agonists) is quite controversial. There have been conflicting reports of the therapeutic value of such therapy in patients with HRPC,^{29,30} and, clearly, the side effects of hormonal therapy may negatively impact on quality of life. At our center, we have favored the continued use of LHRH agonists in patients receiving systemic therapy because of the theoretical advantage of suppressing cancer cell subpopulations that may retain androgen-responsiveness.

Next, full staging of the patient, utilizing cross-sectional imaging and bone scan, is necessary at the time of treatment. Knowledge of the disease burden, location, and symptomatology will be essential in planning treatment. At our center we have gener-

ally obtained a baseline magnetic resonance imaging of the spine in individuals with known spinal metastases in order to rule out sub-clinical epidural compression.

An evaluation of the lower urinary tract may allow the correction of a noted dysfunction and also identify individuals at risk of compromise of the lower or upper tract. In some cases, prophylactic medical therapy can be instituted. In others careful follow-up monitoring can be planned. Decisions regarding the need for surgical intervention or upper-tract drainage should be made before

instituting systemic therapy.

Finally, if a patient is deemed an acceptable candidate for systemic therapy, based upon the above criteria, a treatment regimen can be selected. In general, at our center, we have opted for a taxane-based regimen as first-line therapy, given its excellent overall response rates and tolerability. The treatment regimen obviously may be individualized, based upon the underlying medical condition of the patient.

In following patients, it is useful for the patients to continue interacting with physicians in each of the involved disciplines. Psychosocial demands, for example, may continue to evolve as the treatment or disease progresses. Similarly, careful monitoring of lower urinary tract function, neurologic function, and pain are important components of ongoing care. Patient education, including nutritional counseling and information regarding complementary medicine, generally proves useful as well; maintenance of bone stability, for instance, can be aided through the use of bisphosphonates concomitant with cytotoxic therapy. Finally, clinical trials can be implemented at the time of progression on a standard regimen. ■

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Main Points

- Traditionally, management of patients with hormone-refractory prostate cancer (HRPC) has been palliative, including the control of pain and some preservation of quality of life.
- With the development of potentially efficacious chemotherapeutic regimens, particularly taxane-based chemotherapies, physicians are focusing on providing systemic therapy for the control of disease combined with aggressive local therapy for the relief of symptoms.
- Because the needs of patient with HRPC are complex, optimal treatment requires multidisciplinary management of the patient and multimodal approaches to evaluation and therapy.
- Interaction among treating physicians, specialists in disease processes and pain management, and supportive and ancillary services provides a comprehensive treatment strategy that addresses the individualized needs of the patient.